REMARKS

Restriction under 35 U.S.C. 121

I. Restriction and Election with Traverse

Claims 1-140, 142, and 143 are withdrawn without prejudice. Newly amended claims 141 and 144 now stand ready for examination.

The Office has stated the following:

> Restriction to one of the following inventions is required under 35 U.S.C. 121.
>
> Group I: claims 1-55, 112-137, 142 drawn to methods and compositions for treating tumors employing an enhanced combination of a cyclooxygenase-2 inhibitor, an Integrin antagonist and an antineoplastic agent.
>
> Group II: claims 56-111 and 138-140 drawn to methods for treating tumors employing and enhanced combination of radiation alone with the group I combination.
>
> Group III: claims 141 and 144 drawn to methods for treating tumor employing an enhanced combination of a cyclooxygenase-2 inhibitor and an Integrin antagonist.
>
> Group IV: claim 143 drawn to a method for treating tumors employing radiation with the enhanced combination of group III.

The Office has further stated that:

> If applicants elect groups I-IV, applicants are, therefore, required to elect a single enhanced combination of one cyclooxygenase-2 inhibitor with one Integrin antagonist with or without one antineoplastic agent. The neoplastic agents are classified in both class 514 and class 424. For example, cisplatin is in class 424 subclass 649, doxorubicin is in class 514, subclass 34 and paditaxel [paclitaxel] is in class 514, subclass 449.

In response to the restriction, Applicants have elected Group III from Groups I-IV above without traverse.

With traverse, Applicants elect celecoxib as the single cyclooxygenase-2 inhibitor. With traverse, Applicants elect (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine as the single integrin antagonist.

Support for the election of the integrin antagonist, (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine and for the cyclooxygenase-2 inhibitor, celecoxib is found on numerous pages throughout the application.

The use of celecoxib is described particularly on page 236, lines 1-4; page 258, lines 11-14, page 273, lines 1-5, and page 292, lines 1-3 of the present application.

Support for the use of the integrin antagonist, (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, is found on page 241, lines 6-10, page 279, lines 7-9, page 311, lines 6-10, and page 337, lines 1-4 of the present invention.

II. Reasons for traverse

Applicants respectfully traverse the restriction for the following reasons:

A. Applicants point out that the elected compound, celecoxib, and the non-elected compounds of the claims comprise a single family of compounds having activity as cyclooxygenase-2 inhibitors. The unifying feature of this class of compounds is the cyclooxygenase-2 inhibitory activity, which is common to all cyclooxygenase-2 inhibitors of the present invention. Representative compounds of the defined family possess cyclooxygenase-2 activity, as described in the present application on page 259, lines 7 to 18. The phrase reads as follows:

> The phrase "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" or "cyclooxygenase-II inhibitor" includes agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of cyclooxygenase-1. Preferably, it includes compounds which have a cyclooxygenase-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM.

Therefore, the cyclooxygenase-2 compounds are not independent and distinct, each from the other. Accordingly, the Applicants point out that no restriction is appropriate among the compounds recited, and respectfully request that the Restriction Requirement for the cyclooxygenase-2 inhibitors be withdrawn.

Similarly, the Applicants point out that the integrin antagonists are not independent and distinct, each from the other. Applicants point out that the elected compound, (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, and the non-elected compounds of the claims comprise a single family of compounds having activity as Integrin antagonists.

The unifying feature of this class of compounds is the integrin antagonistic activity, which is common to all integrin antagonists of the present invention. Representative compounds of the defined family possess integrin antagonistic activity, as described in the present application in Table 1, line 20. Further description of the integrin antagonists can be found of page 34, line 13 through page 35, line 15.

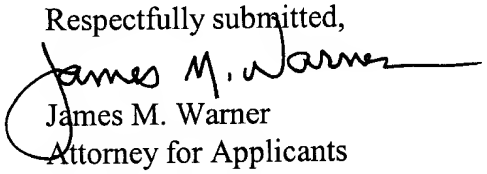
Therefore, the integrin antagonistic compounds are not independent and distinct, each from the other. Accordingly, the Applicants assert that no restriction is appropriate among the compounds recited (for the cyclooxygenase-2 inhibitors and integrin antagonist compounds), and respectfully request that the Restriction Requirement for these to be withdrawn.

III. Election is without prejudice

Applicants submit that the provisional election of celecoxib from the list of cyclooxygenase-2 inhibitors, and (3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine, from the list of integrin antagonists, is without prejudice to Applicants' right to file divisional applications directed to the subject matter not contained therein.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, he is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,



James M. Warner
Attorney for Applicants
Reg. No. 45,199
PHARMACIA CORPORATION
Corporate Patent Law Department
314-274-3642 (St. Louis)